REMARKS

Claims 1 and 3-27 are pending in the application. Claim 26 has been amended for clarity. Support for the amendment can be found in the original claims as well as throughout the specification. No new matter has been added.

Rejections Under 35 U.S.C. § 103(a)

The subject matter of the various claims was commonly owned at the time the inventions covered in the application were made.

Claims 1, 3-12, 15-27 are rejected under 35 U.S.C. §103 as being unpatentable over Passmore et al., US 5,976,846 (Passmore). The present claims are directed to a method of constructing a DNA library of vector molecules, each vector molecule including a different library element encoding region that encodes a naturally occurring sequence. The method includes allowing homologous recombination (HR) and gap repair to occur in vivo between a vector and a nucleic acid insert containing a library element encoding region, where the vector and the insert have first and second common regions that allow HR to occur. Passmore discloses a method of "multi fragment in vivo cloning" used to map mutations (See Passmore abstract and column 24, lines 20-21 (24:20-21), emphasis added). Passmore never refers to the use of the constructs in producing a library. In fact, Passmore does not mention the term "library" at all.

The Examiner provides the following basis for the rejection:

> Passmore et al. disclose that the cloning method is based on the ability to create a series of overlapping DNA fragments by introducing at one end of each DNA fragment a sequence element homologous to the next DNA fragment in the series (see fig. 1). Nevertheless, the final DNA fragment to be inserted into vectors have one end of the DNA fragments which is homologous to one end of the vector and another end of the DNA fragments which is homologous to another end of the vector (see Fig 4) and then in vivo homologous recombination is taken place. Thus, the teachings of Passmore et al. suggest some limitations in claims 1, 3 and 26 that the DNA insert molecule has a first common region which is homologous with the first region of the vector molecule, a second common region which is homologous with the second region of the vector and a library element encoding region disposed between the two common regions.
>
> Therefore, one of ordinary skill in the art at the time of the instant invention would have been motivated to apply the method of Passmore et al. to make the instant invention with a reasonable expectation of success because the method of

> Passmore et al. is superior to previous methods in which it does not require the use of any specific DNA restriction or modification enzyme in vitro, other than those in the PCR process, can be used to recombine mutations present on separate DNA inserts into a single new insert, carried on a cloning vector (See column 3, lines 31-34 and lines 41-47). The method of Passmore et al. also can be used to construct vector that stably transform yeast (See column 3, lines 54-67) (as recited in claim 7). It would have prima facie obvious to carry out the method as claimed.

This rejection is respectfully traversed. To establish prima facie obviousness of a claimed invention, the prior art must teach or suggest all the limitations of the claims, and the motivation to arrive at the present invention and a reasonable expectation of success must be found in the prior art. In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991). In this instance, a prima facie case of obviousness has not been made because the cited references, alone or in combination, fail to disclose or suggest a method of constructing a DNA library by allowing homologous recombination HR to occur in vivo between a vector and a nucleic acid insert that contains a library element encoding a naturally occurring sequence. Nor does the art provide a motivation for a skilled artisan to modify Passmore to arrive at the presently claimed methods. Indeed, the art in fact teaches away from the present claims, as discussed below.

The present claims recite homologous recombination between first and second regions of a vector that are homologous to first and second regions flanking a naturally occurring library element encoding region in an insert molecule. Thus, the present claims require homologous recombination between two DNA molecules, a vector and an insert. Contrary to the Examiner's suggestion, Passmore's Fig.4 does not disclose or suggest homologous recombination between two DNA molecules. The discussion of Fig. 4 provides that "regions of overlap that allow homologous recombination in vivo are each indicated by an X. The pairs of gene fragments that are recombined in vivo are shown (Passmore 27:15-18). As can be seen, Fig. 4 shows recombination (X's) between three DNA molecules, not two molecules. That is, elements 108, 110 and 112 of Fig. 4 are recombined together. There is no single insert that is recombined with the vector, as recited in the present claims. Indeed, all of the Passmore methods require construction of a yeast vector to be "assembled from three (or more) component parts" (Passmore 9: 41-42, emphasis added). Therefore, the first criterion for a prima facie case of

obviousness has not been met, as the cited reference does not disclose all the limitations of the claims.

Nor does the cited art provide a motivation to modify Passmore to arrive at the presently claimed methods. To the contrary, Passmore sees a disadvantage in a method that allows the recombination of only two DNA molecules, thereby teaching away from the present claims. For example, Passmore characterizes a method of Degryse et al. as follows: "This method can be used to join at most 2 DNA molecules; this is a significant disadvantage" (Passmore 3:18-21, emphasis added; see also 2:22-25). Because Passmore et al. clearly sees a disadvantage in using two DNA molecules, Passmore actually teaches away from the present claims, which specify recombination of two component parts, a vector and an insert. Therefore, the second and third criteria for a prima facie case of obviousness are also lacking because the Examiner has not provided a motivation or a reasonable expectation of success for one of ordinary skill in the art to modify Passmore in any way, much less in a manner as to arrive at the claimed methods. Accordingly, a prima facie case of obviousness has not been made.

In another aspect, claims 23-26 are rejected under 35 U.S.C. §103 as being unpatentable over Passmore. The Examiner provides the following basis for the rejection, "Passmore et al. also disclose two hybrid screening system (See column 21, lines 27-43) in which the teachings of Passmore et al. are inherent that the limitations of claims 23-26 are suggested." Claim 26 has been amended to clarify the relationship of the elements to be recombined in the claimed method. This aspect of the rejection is respectfully traversed with respect to the present claims. Claims 23-26 require recombination and gap repair to occur in each of the plurality of host cells between a nucleic acid insert and a vector. As discussed in detail above, Passmore does not teach, suggest, or provide a motivation to arrive at the claimed methods reciting recombination of two component parts, i.e., a vector and an insert. If anything, Passmore teaches away from a method that involves recombination of only two component parts. Therefore, the Examiner is respectfully requested to reconsider and withdraw this grounds for rejection.

In another aspect, claims 13-14 are rejected as unpatentable over Passmore et al. in view of Fraser et al., U.S. Patent No. 4,870,023 (Fraser). This rejection is respectfully traversed.

Claims 13-14 limit claim 1 by reciting that the first and second common regions are produced by the ligation of adapters. As discussed above in detail, there is no teaching or suggestion in Passmore of methods for constructing an in vivo DNA library, as presently claimed. Fraser fails to make up for the deficiencies in Passmore. Fraser discloses a recombinant baculovirus construct which encodes fusion polyhedrin proteins capable of forming occlusion bodies containing foreign peptides. The recombinant baculoviruses are formed by insertion into or replacement of regions of the polyhedrin gene that are not essential for occlusion body formation with exogenous DNA fragments. There is no teaching or suggestion in Passmore or Fraser, alone or in combination, describing the vector/insert combination involving two DNA molecules recited by the present claims, its use to generate an in vivo DNA library, and the screening of this in vivo DNA library. Therefore, Applicants respectfully request that this rejection be withdrawn.

In view of the foregoing claim amendments and remarks, it is respectfully submitted that the application is in condition for allowance.

Attached is a marked-up version of the changes being made by the current amendment. Enclosed is a Petition for One Month Extension of Time.

Applicant asks that all claims be allowed. Enclosed is a $55.00 check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 29 October 2002

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Version with Markings to Show Changes Made

Claim 26 has been amended as follows:

26. (Amended) A method of constructing a DNA library for screening in a two-hybrid system, comprising:

providing a plurality of nucleic acid molecules, wherein each of the plurality of nucleic acid molecules includes, in order from 5' to 3', a first common sequence, a library element encoding region, and a second common sequence;

providing a plurality of first primers, each of said first primers having a first region which hybridizes to said first common sequence of said nucleic acid molecule and having a second region which does not hybridize to said first or second common sequence;

providing a plurality of second primers, each of said second primers having a first region which hybridizes to said second common sequence of said nucleic acid molecule and having a second region which does not hybridize to said second or first common sequence;

forming a reaction mixture which includes the plurality of nucleic acid molecules, the plurality of said first primers, and the plurality of said second primers, under conditions which provide a plurality of nucleic acid insert molecules having the following structure, in order from 5' to 3', a second region of the first primer/the first common region/a library element encoding region/the second common region/a second region of the second primer;

providing a plurality of host cells;

providing a vector having a first region which is homologous with the second region of the first primer, and a second region which is homologous with the second region of the second primer, wherein said vector further includes a transcription factor activation domain;

introducing a vector molecule into each of each host cell of said plurality of host cells;

introducing one or more of the nucleic acid insert molecules into each host cell of said plurality of host cells under conditions which allow for recombination and gap repair to occur in each of the plurality of host cells between one of the plurality of nucleic acid inserts and the vector;

introducing into each host cell of said plurality of host cells a nucleic acid molecule encoding a hybrid protein, wherein the hybrid protein includes a transcription factor DNA-binding domain attached to a test protein;

introducing into each host cell of said plurality of host cells a detectable gene, wherein said detectable gene comprises a regulator site recognized by the DNA-binding domain and wherein said detectable gene expresses a detectable protein when the test protein interacts with a protein encoded by the DNA library;

plating each host cell of said plurality of host cells onto selective media; and

selecting for each host cell of said plurality of host cells containing a DNA encoded protein which interacts with test protein.